DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Rese
1401 Rockville Pike
Rockville MD 20852-1448

CBER-98- 010

WARNING LETTER

12-16-97

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Tatsuto Yamamoto
Responsible Head
Seikagaku Corporation
1-5 Nihonbashi-honcho 2-chome
Chuo-ku, Tokyo 103 Japan
U.S. License Number 1179

Dear Mr. Yamamoto:

An inspection of Seikagaku Corporation facility, located at 258-5 Aza-Matsukubo, Oaza-Akahama, Takahagi-shi, Ibaraki 318 Japan, was conducted from September 22 through September 25, 1997. During the inspection, our FDA investigators documented significant deviations from the applicable standards and requirements of Subchapter F, Parts 600-680, and Subchapter H, Parts 809 and 820, Title 21, Code of Federal Regulations as follows:

1. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75], in that:

   a. The Tachypleus Amebocyte Lysate (TAL) LS-20 production process has not been validated nor has a validation protocol been established.

   b. The acceptance criteria specified in the lyophilization validation protocol is limited to moisture testing of the finished product and does not include various operating parameters such as pre-cooling, freezing, and primary/secondary drying.

   c. No validation studies or routine testing has been performed with respect to container/closure integrity [21 CFR 600.11(h)].

d. Media fills for TAL are not performed routinely; media fills have been performed on February 1992 and August 1997.

e. The two ovens used for depyrogenation of product vials and manufacturing glassware and the three autoclaves used to sterilize rubber stoppers where initially validated in June 1992 and have not been revalidated.

2. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications including documented instructions, standard operating procedures (SOPs), and methods that define and control the manner of production [21 CFR 820.70(a)(1)], in that:

a. The blending speed of substrate and excipients is neither defined or recorded.

b. The stability program for lyophilized TAL LS-20 does not include moisture testing.

c. There is no SOP for the performance of visual inspections of filled, lyophilized products.

3. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications including monitoring and control of process parameters and component and device characteristics during production [21 CFR 820.70(a)(2)], in that blending studies have not been performed to ensure the substrate/excipient blend remains uniform after mixing and during filling.

4. Failure to establish and maintain procedures for receiving, reviewing, maintaining, and evaluating complaints by a formally designated unit [21 CFR 820.198(a)], in that there is no formal system for documenting and tracking complaints.

5. Failure to maintain a device history record to demonstrate that the device is manufactured in accordance with the device master record [21 CFR 820.184 and 600.12], in that the calculation for product accountability before and after filling to ensure vials have been accurately filled is not documented on the batch production records.

6. Failure to ensure that all equipment used in the manufacturing process meet specified requirements [21 CFR 820.70(g)], in that the bacterial retentive filter, used in the lyophilizer for sterilizing nitrogen during vacuum breaks, is not integrity tested after use.

We acknowledge receipt of your written response dated October 22, 1997, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. The following represent our comments regarding your response.

FDA 483 item # 3B & C
We acknowledge your commitment to establish height ranges for seating stoppers prior to lyophilization. Please note that the range of 4mm - 6.5mm for stopper heights should be addressed in your validation studies to ensure products lyophilized at stopper heights between 4mm - 6.5mm comply with acceptance criteria in every respect. In addition, please be advised of the necessity for an accurate TAL accountability in that production losses for each batch of TAL need to be determined.

FDA 483 item #4B
Please define the temperature range that will be used to pre-cool the shelves.

FDA 483 item #4D
We acknowledge your commitment to perform integrity testing of nitrogen filters, however, we request that the current filter be integrity tested prior to the next use in order to demonstrate filter integrity. In addition, please describe the method used for integrity testing of the filters.

FDA 483 item #6
Please provide the details for the container/closure integrity testing including the planned number of batches as well as the number of units that will be tested per batch. Additionally, please define the temperatures and incubation times which will be used.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies at your facilities. It is your responsibility as management to assure that your facilities are in compliance with all the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of (any additional steps) specific steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, license suspension, and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610.

Sincerely,

for, James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research